Human Vaccines & Immunotherapeutics

ISSN: 2164-5515 (Print) 2164-554X (Online) Journal homepage: http://www.tandfonline.com/loi/khvi20

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To cite this article: Giuseppe La Torre, Alice Mannocci, Rosella Saulle, Vittoria Colamesta, Angela Meggiolaro, Daniele Mipatrini & Alessandra Sinopoli (2016): Economic evaluation of HBV vaccination: A systematic review of recent publications (2000-2013), Human Vaccines & Immunotherapeutics, DOI: 10.1080/21645515.2016.1166328

To link to this article: http://dx.doi.org/10.1080/21645515.2016.1166328

Accepted author version posted online: 22 Apr 2016.

Economic evaluation of HBV vaccination: A systematic review of recent publications (2000-2013)

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Abstract

Aim: To conduct a systematic review of the economic evaluations (EE) of HBV vaccination, taking also into account the studies published in the new millennium.

Methods: An extensive scientific literature review was conducted using two electronic medical journal databases: Scopus and PubMed engines for published studies on EE of HBV vaccination.

Results: 22 articles were reviewed, 9, 5 and 8 cost-effectiveness, cost-benefit and cost-utility analysis, respectively. Studies were mainly concerning EE of universal vaccination (UV), mostly with regards to low or low-medium income countries. For high income countries, EE were focused on the possible implementation of HBV vaccination in particular settings, such as diabetic, renal and other chronic conditions care, as well as infectious diseases.

UV has usually a very good cost-effectiveness ratio (80%), ranging from cost-saving (*China*) or few Euro per LY/QALY gained (in Thailand, and Vietnam) to 630.00$/QALY in USA (Asian and Pacific Islands).

Moreover, EE of HBV vaccination are favorable in the infectious diseases field as well as for chronic conditions. In relation to diabetes the studies gave controversial results.

Conclusion: This systematic review highlighted the importance of introducing HBV vaccination not only for infant UV program but also for other settings in which patients are people are affected by communicable and non-communicable diseases.

Introduction

It is well recognized that Hepatitis B virus (HBV) is one of world's most common blood-borne viral infection, chronically infecting hundreds of million people worldwide [1]. Moreover, there is evidence that it is responsible for substantial morbidity and mortality and is together with HCV a leading cause of hepatocellular carcinoma [1]. It is estimated that nearly 2 billion people worldwide have been infected with HBV; of these, 360 million are chronically infected, and among them 600000 individuals die each year from HBV associated liver cirrhosis or hepatocellular carcinoma [2].

According to Drummond [3] the economic evaluation can be defined as the comparative analysis of alternative courses of action in terms of both their costs and consequences, and the first attempts to consider economic issues related to HBV vaccination date back to early ’80 [4], and particular attention was posed on health care personnel (HCP) (i.e., renal dialysis, blood transfusion centres, clinical biology laboratories, surgery, anaesthesia, closed psychiatric institutions and others), finding that the financial investment has proved economically beneficial for the insurance fund. In fact, we must recognized that, since HBV is transmitted primarily through blood and sexual routes, in a way that is similar to HIV and hepatitis C virus (HCV) [5], it must be considered an occupational hazard for HCPs [6]. Moreover, according to Di Giuseppe et al [7] HCPs are at risk of blood-borne, airborne, and droplet-spread transmission of infectious agents, and this is particularly true due to frequent and often intensive occupational exposures, among which it can be included percutaneous injury, contact with mucous membranes, or nonintact skin with blood or other potentially infectious bodily fluids [8-10]. On the other hand , HCPs can also act as potential paths of nosocomial transmission of several infections to patients and other close contacts.

Beutels underlined that in areas of low, intermediate and high endemicity of HBV infection, the universal vaccination seems justifiable on the basis of economic evaluation. However, he noted that the accuracy of the models has improved

over the years, even if some improvements have been made, further steps are required, especially concerning transparency, completeness and comparability of analyses [11]. Furthermore, Tu et al. very recently reviewed this issue applied to developing and less developed countries, finding that the almost totality of the studies the implementation of universal immunization against HBV is capable to reduce the level of endemicity of hepatitis B, and probably cost effective in many settings [12].

As far as concerns infant vaccination importance, it is well known that infants infected with hepatitis B virus (HBV) face the risk of developing severe complications [13] and childhood chronic HBV infection prevalence has been markedly reduced in those counties where vaccination policies have been put in place [14-17].

In accordance with the World Health Organization [18] recommendations, all infants should receive their first dose of the hepatitis B vaccine immediately after birth, preferably within 24 hours.

The availability of a vaccine against HBV infection let the disease effectively preventable in a safe and effective way since 1982 [19]. As of 2011, hepatitis B vaccine has been incorporated in 179 countries' national infant immunization programs, and about 69% of the 2008 birth cohort received all three doses of the vaccine [19]. Nevertheless, while the vaccination coverage of three doses at the world level is 75%, many differences do exist between countries and macro-areas (Table 1), with lower coverage in South-East Asia (57%) and African (71%) WHO regions.

At the beginning of the '90 Bloom et al. [20] found that the strategy of universal newborn vaccination alone leads is cost-effective (incremental cost-per-year-of-life saved of $3.332), and the same results were found by Holliday and Faulds [21]. However, other studies found that mass vaccination of adolescents were more cost-effective [22] or at least as cost-effective as the universal vaccination for infants, over a wide range of assumptions [23], but no cost-saving [24].

Further, it was clear that the majority of the cost of HBV vaccination program is due to the cost of the vaccine (more than three fourth of the cost of introducing HBV vaccine) [25, 26].

Mass vaccination for health care workers was an issue since the availability of HBV vaccination, and this option was considered more beneficial than costly[27-29], and now must be considered all over the world also for ethical and social, as well as for economic aspects [30]. There is also evidence that preventing the transmission of HBV infections in dialysis centers is possible with the administration of HBV vaccine to susceptible patients and staff [31].

Essentially, the need to go beyond the infant universal vaccination, i.e. to vaccinate older age groups, including adolescents and adults, is determined by the burden of disease (HBV infection) in a specific country [32]. Italy was one of the first countries (1991) that, in order to reduce the HBV related pathologies in the Italian population, implemented a multi-level approach, including the universal vaccination of newborn babies, 12-year old adolescents and high risk groups [33]. The effect of this vaccination strategy was impressive, reaching two main goals, i.e., protecting susceptible people from the infection caused by the hepatitis B virus and reducing the virus circulation in the population [34].

Thus, the objective of this paper is to conduct a systematic review of the economic evaluations of HBV vaccination, taking also into account the studies published in the new millennium.

Results

Data extraction

The information extracted were: references, publication year and type of analyses, alternatives, nation/ perspective, sample, efficacy measures/cost measure and results. The characteristics of each study are shown in Table 3.

Identification of relevant research

Using the aforementioned inclusion criteria the following articles were found (see Fig 1. Flow-chart):

- 211 articles for *Pubmed* search;
- 276 articles *for Scopus* search;

A total of 487 articles were found for all strings, of which 392 were removed because were duplicates in two or all search engines. Moreover, 51 articles were excluded because they were not relevant. At the end of the evaluation, 44 articles met the pre-determined criteria described above, and 22 were included in the systematic review process [35-56].

Type of Economic evaluation of the included studies

The 22 articles reviewed are shown in Table 2.

The classification of the studies is based on the type of economic evaluation:

- CEA (cost-effectiveness analysis) was performed in 9 economic evaluation studies [36, 38-40, 43, 44, 47, 50, 53];
- CBA (cost-benefit analysis) was evaluated by 5 studies [35, 37, 46, 48, 51];
- CUA (cost-utility analysis) was considered in 8 studies [41, 42, 44, 49, 52, 54-56].

The population and the countries considered were different in the studies: 5 analyses were conducted in Europe (Bulgaria, Germany, Ireland and UK), 8 in America (all in the USA), 7 in Asia (China, Iran, South Korea Taiwan, Thailand, Vietnam), 1 in Africa (Mozambique) and 1 in Oceania (Australia).

Sample and results

The majority of the studies were concerning economic analysis of universal vaccination (12; 54.5%), mostly with regards to low or low-medium income countries (7; 58.3%). Moreover, it is interesting to note that in studies on high income countries, the economic evaluations were focused on the possible implementation of HBV vaccination in particular settings, such as diabetic, renal and other chronic conditions care, as well as infectious diseases (Sexually transmitted diseases, HIV counseling, HCV patients, injection drug users).

So the results of this systematic review are heterogeneous. Concerning the universal vaccination, this has usually a very good cost-effectiveness ratio (80%), ranging from cost-saving (*China*) [56] or few Euro per LY/QALY gained (in Thailand, and Vietnam) [40, 52] to 630.00 $ /QALY in USA (Asian and Pacific Islands) [42].

There is clear evidence that all infants should receive their first dose of hepatitis B vaccine as soon as possible after birth, preferably within 24 hours [2].

As suggested by WHO the universal HBV vaccination represents a comprehensive approach to eliminating HBV transmission that considers infections acquired perinatally and during early childhood, but it is important to consider also other settings that involve different pattern of transmissions and different populations (teenagers and adults) [2]. In fact, as far as concerns the other settings, the economic evaluations of HBV vaccination are favourable in the infectious diseases field as well as for chronic conditions. The HBV vaccination could be of great interest and impact in settings that involve injection drug users (IDUs) and jails, where HBV infections could be present and rapidly spreading [57-58], alone or together to other viruses (HIV, HCV). In this cases, the accelerated vaccination schedule could easily improve hepatitis B vaccination adherence among IDUs [59], as well as the use of the standard vaccine regimen (0, 1, 6 months) is capable to may induce higher levels of antibody to the virus comparable to those induced by regimens of four injections of either standard or double doses [60].

In relation to diabetes the economic evaluations gave controversial results, reflecting what happens for the clinical recommendation. In 2011, the Advisory Committee on Immunization Practices (ACIP) recommended that all previously unvaccinated adults aged between 19 and 59 years with diabetes mellitus (both type 1 and 2) be vaccinated against hepatitis B as soon as possible after a diagnosis of diabetes is made (recommendation category A). On the other hand, data on the risk for hepatitis B among adults aged 60 years and over are less robust, so that this group of patients could

be vaccinated at the discretion of the treating clinician, only after the assessment of the risk and the likelihood of an adequate immune response to vaccination [61]. Concerning the economic evaluations, while Kuan et al [55] found an acceptable incremental C/E (12.613$/QALY),this did not happen for Hoerger et al [54].

As far as concerns the quality of these economic evaluations, using the weighted scale of Drummond, very high scores were found (median 91.5; range: 53-98) with the vast majority of the papers (90.9%) with score over 80 (Table 2).

Discussion

In this systematic review a wide range of results in terms of economic evaluations of HBV vaccination was found, especially regarding the way for measuring the efficacy/effectiveness. From the methodological point of view, cost-utility and cost-effectiveness analysis are almost equally represented. In order to be more adherent to commonly used cost-utility analysis performed in the biomedical field, future studies will address better the way in incorporating a quality weighted measure of effectiveness, such as QALY (Quality Adjusted Life Years). This kind of studies will be of crucial importance in order to convince decision makers to implement the HBV vaccination programs in the public sector.

Moreover, in this review we found five single studies in which costs and effectiveness were measured in the same way (money), and this is in line with the actual trends of the economic evaluations that use less frequently cost-benefit analysis.

Concerning possible limitation of this study, it must be recognized that there is a lack of information in many countries/continents, considering that a single study exists coming from Africa and no one from Southern and Central America. Anyway, this is not surprising, given the very low number of randomized clinical trial conducted in these continents [62-68].

Some final considerations must be underlined. Since Hepatitis B infection and related diseases are considered an important hazard for the general population and for many workers, not only in the health sector, the economic impact is relevant (69-70).

There is evidence that the virus transmission usually occurs through blood as well as blood products, and other body fluids (saliva, semen, et cetera). Different situations could be the case of transmission, such as sexual intercourse, illicit drug use with shared needles, above all heroin, blood transfusions or use of blood products. Moreover, HBV infection is one of the mail virus transmitted by medical practices, such as surgical intervention, dental care, especially in cases where infection control precautions are inadequate (71-80).

The infections sustained by HBV mainly affect the liver, causing acute and chronic diseases, such as liver infections and cirrhosis (73).

It is now well known that chronic infections with HBV hepatitis C virus (HCV) are also considered the main cause of liver cancer and for this fact classified by the International Agency for Research on Cancer (IARC) as carcinogenic to humans (group 1) (74).

According to WHO forecast, the infections caused by HBV will be the third cause of death for infectious diseases in 2030 in the industrialized countries (75). Viral hepatitis, and among which those caused by HBV, knows no borders (76).

The epidemiology of HBV related pathologies is continuously changing. As a typical example the waste management field is a field of increasing interest, considering the vulnerability of recyclable general waste collectors to HBV infection, as well as the medical waste handlers. There is sufficient evidence that witnesses HBV immunization, as well as post-

exposure protection of medical waste handlers, in addition to proper management of medical waste by the health authorities, might reduce the risk of acquiring infectious agents by this type of workers in a significant way (77). Additionally, we must consider in this field also that the need to use HBV vaccine prophylaxis in this category of workers is important for avoid possible medical legal litigations (78-79).

In this field the importance of public health policies that address the health and safety of this socially vulnerable population is very high (80-82).

A very recent systematic review highlights that waste workers need to be vaccinated against HBV infection taking into account these workers are at risk of acquiring this infection through the exposure to potentially infected waste (83).

The HBV vaccination has also and indirect effect on the epidemiology of blood transmitted diseases (BTD). In fact, there is evidence that significant improvements in the screening process of BTD of both donors and household contacts is fundamental in order to minimize the infectious risk (84-85).

Moreover, a very good field for reducing the HBV burden through the HBV vaccination is concerning men who have sex with men, and Commercial sex workers, among which there exist a disproportionate burden of hepatitis B virus (HBV) infections (86-95).

The WHO recommendations include the offer the rapid HBV vaccination regimen for persons who inject drugs (96-97).

As far as concerns one of the strengths of this review, a gap has been filled, since it was shown the use of economic evaluations n highly endemic areas, that was lacking in previous reviews [11], and this is very important to raise both public awareness of the effectiveness and economic attractiveness of universal immunization against HBV [52].

Conclusion

In conclusion, this systematic review highlighted the importance of introducing HBV vaccination not only for infant universal vaccination program but also for other settings in which patients are people are affected by communicable and non-communicable diseases.

HBV infection causes at the world level a high burden in terms of costs, both direct and indirect (987-120).

In accordance with Beutels [11] it must be recognized that the role of economic evaluations of HBV vaccination in the decision-making process could be important, but the economic evaluation is only one of several elements that can have an influence on the introduction of a specific vaccine policy in a given country, including issues such as medical, epidemiological, organizational and ethical aspects. There is sufficient evidence that, after the cases of HPV (121-123), influenza and pneumococcal vaccinations (124-125), there is the need for a full health technology assessment (HTA) (126) also for HBV vaccination. As suggested by NICE international (127), HTA should always be part of the priority-setting process, and this is particularly true in the field of vaccinations, in order to give efficient and equitable allocation of health care in the field of prevention.

Materials and methods

Identification of relevant studies

A scientific literature review was conducted considering the period 2000-2013 and using two electronic medical journal databases: Scopus and PubMed engines for published studies on economic evaluations of HBV vaccination.

The keywords used were the following:

"HBV", "vaccination", "cost-effectiveness", *"cost utility", "cost-effectiveness", "cost benefit" and "economic evaluation"*.

Search criteria and the flow-chart of the results are summarized in Figure 1.

No date and language restrictions were applied for the selection of the papers published. Further, all studies focused on the economic evaluation of HBV vaccination were selected, without any limitation of population and country.

The review process, including search and selection (identification, screening, eligibility of included studies) was performed according to the PRISMA criteria [128] (Figure 1).

In the selection process, abstracts were initially read to identify potentially eligible full text papers which were then retrieved and assessed in order to decide on the final inclusion.

Articles were examined and were excluded if:

1) the research was based on considering costs only;

2) studies were not pertaining to HBV vaccination;

3) the full text was not available.

If the electronic databases outcomes overlapped, all duplicate articles were eliminated.

The weighted Drummond's checklist (129) was used to assess the quality of the economic evaluations.

Conflict of interests

The author declares that there is no conflict of interests regarding the publication of this article.

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Table 1 - HBV Vaccination coverage estimates, by vaccine and World Health Organization (WHO) region — worldwide, 2011

WHO region	Vaccination coverage (%)
	3 doses of hepatitis B vaccine
Worldwide	**75**
African	71
Americas	90
Eastern Mediterranean	83
European	77
South-East Asia	56
Western Pacific	91

Table 2. Characteristics of the selected studies by year of publication and types of economic analysis

References	Type of analyses	Alternatives	Nation/ Perspective	Sample	Efficacy Measures/ cost measures	Main Results	Quality assessment score
Wiewiora-Pilecka 2000 [35]	*CBA*	-universal vaccination of all neonates - no vaccination	Poland	Cohort followed for a 20-years period	-Costs -Benefit	In a period of 20 years -no vaccination: loss of 6.318,3 million€ (26.484,2 million zlotys) - vaccination: benefits of €2.873,9 million€ (12.046.4 million zlotys) and losses of 3.444,3 million€ (14.437 million zlotys)	53
Harris al 2001[36]	*CEA*	1.High-risk infants vaccination (65% compliance) 2. universal infant vaccination with Hib-HBV vaccine	Australia	A Markov model simulated the natural history of HBV infection	*1.Direct cost* *2.Incremental cost per life year gained*	*Incremental cost per life year gained = 11.862 $*	*91*

				and disease in an Australian birth cohort (260.000)			
Yang et al 2001[37]	*CBA*	-Prevention (Vaccination, antibody tests, immunoglobulin) - Treatment of HBV-related diseases	South Korea/societal perspective	Costs paid in 1997	Direct and indirect costs	Prevention costs: 142.239 million Won Direct cost for disease: 710.502 million Won Indirect cost for disease: 225.575	89
Saab et al 2002[38]	*CEA*	-routine, annual administration of the vaccine booster to all hemodialysis patients (non-screening strategy) - vaccination based on anti-HBs titers	USA	hypothetical population of 1000 hemodialysis patients followed for 5 years	-costs - effectiveness (i.e. number of HBV infections prevented)	the mean cost per patient prevented: -in the screening strategy US$ 261 - in the non-screening strategy US$ 1129	76

		(screening strategy)					
Adibi et al. 2004 [398]	*CEA*	1.HBsAg screening to find those would-be couples one of whom is HBsAg + and putting seronegative subjects on a protection protocol comprising HBV vaccination, single dose HBIG and condom protection 2.as above plus HBcAb screening in the HBsAg negative spouses of the HBsAg positive persons and giving the protocol only to HBcAb negative	Iran/ societal and healthcare system	Not reported	cost of each chronic infection averted	strategies 1: 202$ per chronic infection averted strategies2: 197$ per chronic infection averted	86

		ones					
Vimolket et al 2005 [40]	*CEA*	-screening for HBsAg, and vaccination (S1) -screening for HBsAg, then HBeAg, and vaccination (S2) -universal vaccination of all neonates (S3) - no vaccination	Thailand	A hypothetical cohort of newborns	-Costs -case prevented	Cost-effectiveness per case prevented -for Strategy 1: € 6.63 (292.79 baht) -for Strategy 2: € 5.99 (264.34 baht) -for Strategy 3: € 3.42 (151.05 baht)	85
Kim et al 2006 [41]	*CUA*	-routine vaccination without screening (V) - screening for antibody to hepatitis B core antigen with an initial vaccine dose during the first visit (SV1) - screening and	USA/ societal perspective	Two hypothetical cohorts of 100,000 adults attending HIV counseling and testing sites	-Cost per QALY gained -Cost per life year gained	ICER V = $4400 both per QALY gained and per life year gained compared with no vaccination SV1 and SV2 = dominated compared with no vaccination	92

		vaccination based on screening results(SV2) -no intervention					
Hutton et al 2007 [42]	*CUA*	-Status quo -Universal vaccination (UV) -Screen and Treat (ST) - Screen Treat and Vaccinate (STV) -Screen Treat and Ring Vaccinate (STRV)	USA	Hypothetical cohort of 10 000 Persons in Asian and Pacific Islands	Costs (2006 U.S. dollars), quality-adjusted life-years (QALYs), and incremental cost-effectiveness	ICER UV = US$ 630.000 ST = US$36.000 STV = US$ 388.000 STRV = US$ 40.000	98
Jakiche et al 2007[43]	*CEA*	-universal vaccination with the combined HAV and HBV vaccine -selective vaccination based on immunity determined by blood testing	USA/Health care systems	Patients with HCV infection belonging to the New Mexico Veterans Affairs health care system	-direct medical costs (2004 US$) - the effectiveness measure was the number of patients immune to both HAV	ICER universal strategy: $154 per additional patient immune to HAV and HBV	93

					and HBV		
Tilson et al 2007[44]	*CEA*	- universal administration of HBV vaccine to all infants -no vaccination	Ireland/national healthcare system	The Markov model of HBV infection is run over a total of 80 cycles of 1 year each. A period of 80 years was chosen as the lifetime period	-Costs -Life years gained	incremental cost effectiveness ratio -for the lowest price of vaccine (€16.65 per course): ICER €10.992/life years gained (LYG) -for the highest price of vaccine (€58.44 per course): ICER €67.200/LYG	90
Hu et al 2008 [45]	*CUA*	-standard vaccination (0,1, 6 months) -accelerated vaccination (0,1, 2 months) -no vaccination	USA/healthcare sector	Cohort of 1964 injection drug users (IDUs)	-Direct costs -Qality-Adjusted Life Years (QALY)	All vaccination strategies were cost-saving compared to the no-vaccination strategy one more than 70% od IDUs had access to medical care	92
Miriti et al 2008[46]	*CBA*	- routine hepatitis B vaccination policy at STD	USA (California and Colorado)	Hypothetical cohort of 2 million STD	***-Direct and indirect costs*** ***-Benefits***	*Costs* -vaccination program: $138	*94*

		clinics -no vaccination		clinic clients accessing services in one year		million -HBV infections occurring: $878 million -clients' time and travel would cost $45 million *Benefits* The net economic benefit (savings) of routine vaccination would be $526 million	
Hung et al 2009 [47]	*CEA*	-universal vaccination -no vaccination	Taiwan/healthcare payer and societal perspectives	Simulation of a birth cohort using 300.000 newborns in 1984	***Incremental cost-effectiveness ratio (ICER)- per life year gained - QALY gained (ICUR)***	The vaccination program dominated over a no-vaccination program, i.e., it is less costly and more effective Societal perspective: ICER= -14.190; ICUR= -13.238 Health care perspective: ICER= -6.126; ICUR = -	96

						5.715	
Fischinger et al 2010 [48]	*CBA*	1.mandatory HBV testing (A1) 2. A1 + nucleic acid testing (A2) 3. A1 + individual donation testing (A3) 4. Time-dependant HBV vaccination (B1) 5. Titre dependent booster vaccination (B2) 6. A1 + B2	Germany	231 whole blood donors and 126 apheresis donors	***1.Direct costs***	A1 over 20 years = €1009 million (base-case) A2 incremental costs of 43% A3 incremental costs of 339% B1 cost reductions relative to A1 of 30% (cost-saving) B2 cost reductions relative to A1 of 14% (cost-saving) B3 incremental costs of 70%	92
Siddiqui et al 2011 [49]	*CUA*	-Universal infant vaccination -Adolescent vaccination -No vaccination	UK	UK lifetime cohort	-costs -QALYs	Universal infant vaccination: £260,000 per QALY gained Adolescent vaccination: £493,000 per QALY gained	95
Klingler et al 2012 [50]	*CEA*	-existing vaccination schedule	Mozambique	Birth cohort of 2008	-Cost -Disability-adjusted life	ICER -for the additional birth dose of 250.95	94

		administered at 6–10–14 weeks -a birth dose vaccination in addition to the existing vaccination schedule			years (DALYs) averted	US$ per DALY averted -sensitivity analysis: 72 US$/DALY averted - 683 US$/DALY averted	
Savova et al 2012 [51]	*CBA*	- cost of immunisation - cost of acute and chronic cases therapy (hospitalization + ambulatory pharmacotherapy)	Bulgaria	Real cases between 1992 and 2010	-costs - Net health benefit (Invested – Averted)	Net health benefit for acute and chronic cases Whole period:€ 14292 (BGN 27927035) Last 10 years: € 70 (BGN 136854)	87
Tu et al 2012 [52]	*CUA*	- universal administration of HBV vaccine to all infants -no vaccination	Vietnam/ national healthcare system	Simulation with a Vietnamese birth cohort using 1,639,000 newborns in 2002	-Costs - Life years gained -QALY -HBV carrier averted	ICER per LYG (US $) from payer's perspective: 4.52 ICER per QALY gained (US $) from payer's perspective: 3.77 Cost of preventing a HBV carrier: 41.79	89

Chen et al 2013 [53]	*CEA*	- universal vaccination (strategy V); - V plus screening for hepatitis B surface antigen (HBsAg) and HBIG treatment for HBsAg-positive mothers' neonates (strategy S) -V plus screening for hepatitis B e-antigen (HBeAg), HBIG for HBeAg-positive mothers' neonates (strategy E); - V plus screening for HBsAg then HBeAg, HBIG for	Taiwan	Hypothetical cohort of neonates of carrier mothers	-costs -infection averted	Strategy S: <$4000 per infection averted for carrier rates >5%. Strategy V: $1400 per infection averted at 30% carrier rate; $3100 per infection averted at 5% carrier rate	91

		all HBeAg-positive, and some HBeAg-negative/HBsAg-positive mothers' neonates (strategy S&E)					
Hoerger et al 2013 [54]	*CUA*	-vaccination of diabetes patients aged 20-59 years - vaccination of diabetes patients aged 60 years and over	USA	Unvaccinated cohort of patients with diabetes	***1.Direct cost 2.acute and chronic HBV infections and complications 3.QALY***	Incremental cost-effectiveness ratio: -vaccinating 20-59 years old: US$ 75.094/QALY vaccinating over 60 years old: US$ 2.7 million/QALY	88
Kuan et al 2013 [55]	*CUA*	-vaccination with HEPLISAV -vaccination with Engerix-B	USA/payer perspective	Hypothetical populations: diabetics, patients with chronic or end stage kidney disease, healthcare workers and	***-Costs - QALY***	ICER Diabetic patients: US$ 12.613 Patients with chronic kidney disease: dominant Patients with end-stage renal disease: dominant Health care workers:	92

				international travelers to countries with high HBV infection prevalence		US$ 11.062 Travellers: US$ 5.564	
Lu et al 2013 [56]	*CUA*	-universal newborn vaccination comprising a timely birth dose (HepB1) - universal newborn vaccination with three-doses (HepB3) - no vaccination	China/ societal or health care payer perspective	cohort of 10,000,000 infants born in 2002	***-Costs*** ***- Life years*** ***- QALY***	Cost saving both for societal or health care payer perspective	95

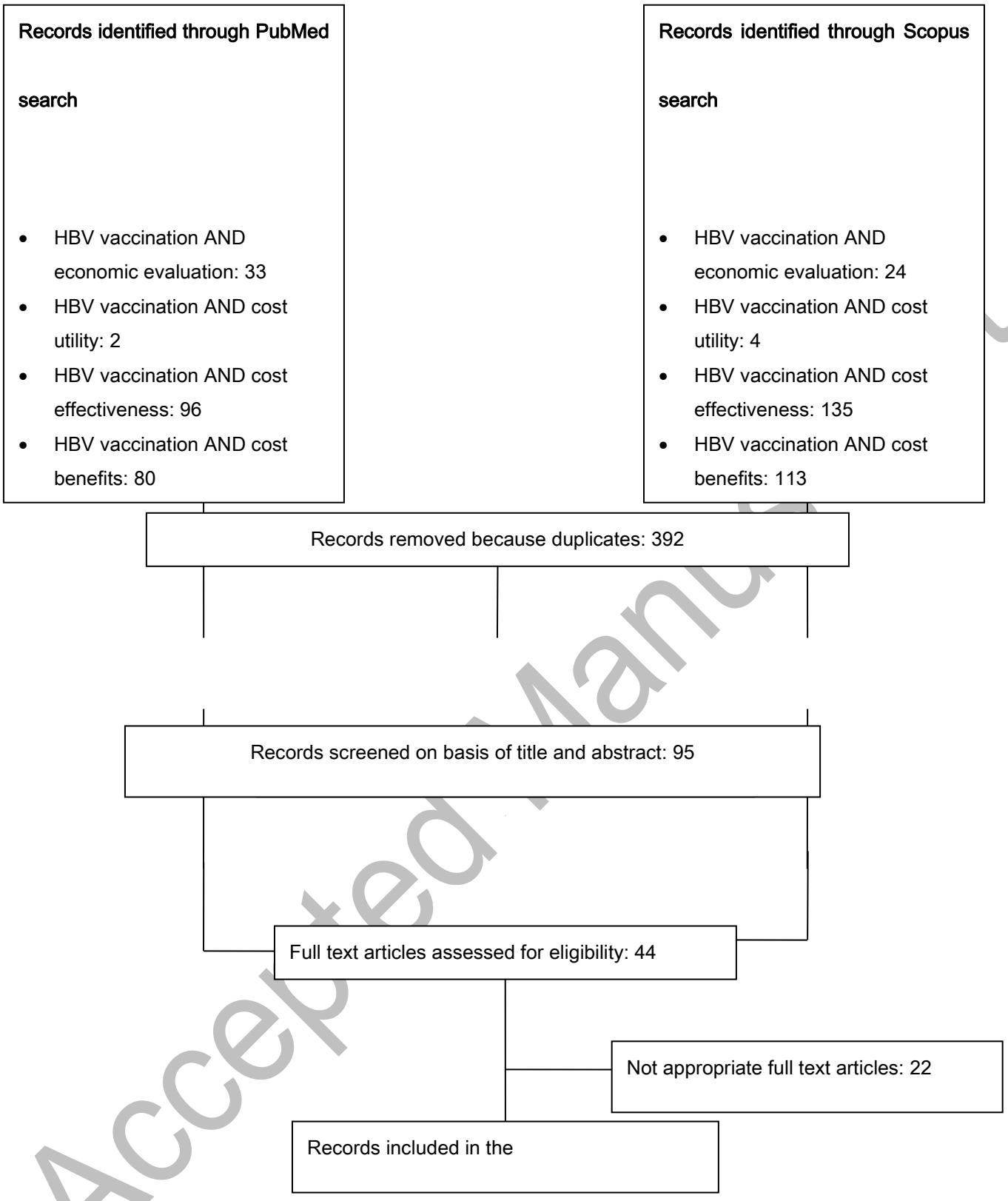

Figure 1